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Global importance of diarrhoeal diseases and malnutration

INTRODUCTION

The amount of new knowledge accumulated in the past 15 years about the aetiology, epidemiology, and public significance of diarrhoeal disease is quite remarkable, particularly because such knowledge has challenged orthodox concepts strongly rooted in misconceptions. Until recently, most diarrhoeas in the general population were regarded as 'food indigestion' and accordingly were given a variety of lay names. Remarkably, even today some medical professionals may refer to certain diarrhoeas as caused by unwholesome food with characteristics incompatible with health. Even though shigellosis, salmonellosis, cholera, giardiasis, amoebiasis, and other specific clinical entities had been characterized satisfactorily, as recently as 10 years ago it was difficult to prove that most outbreaks of diarrhoea in communities were of an infectious origin. In fact, some spoke of 'nutritional diarrhoea' in analogy with nutritional anaemias. It is now accepted, however, that most diarrhoeas in the community and in outpatient and emergency hospital services are related to viral, microbial, and parasitic agents, a concept supported by the following considerations: (a) diarrhoeas are prevalent in ecosystems with inadequate environmental sanitation, education, income, and personal hygiene; (b) secondary cases develop in contacts of index cases within intervals compatible with incubation periods, pointing to spread by direct or indirect contact; (c) incidence and severity of diarrhoea decrease with age, and older persons are relatively free of diarrhoea, suggesting the development of immunity; (d) comprehensive laboratory investigations demonstrate a potential infectious pathogen in about 70 per cent of acute diarrhoea cases (Mata 1983a). Thus, improvement of personal hygiene and environmental sanitation results in a significant reduction in morbidity and mortality due to diarrhoeal diseases. It is easy to understand the epidemic proportions of diarrhoea in New York City at the turn of the century, comparable to that of many less developed countries today, when environmental conditions, education, personal hygiene, and income were low, especially among immigrants.

Part of the gap regarding the aetiology of diarrhoea was resolved in the

last 20 years with the discovery of new agents such as rotaviruses, non-cultivatable adenoviruses, 27 nm agents, caliciviruses, coronaviruses, and enterotoxigenic Enterobacteriaceae (see Mata 1983a). Concomitantly, already known agents were rediscovered in diarrhoea cases, namely, *Campylobacter jejuni*, *Cryptosporidium muris*, and *Yersinia enterocolitica* (WHO 1980). Furthermore, plasmids with the capacity to induce virulence in *Aeromonas hydrophila*, *Klebsiella*, and other Enterobacteriaceae were characterized, while 140 MD plasmid-carrying bacteria were shown to invade the intestinal mucosa causing a dysenteric syndrome.

Proliferation of bacteria in the upper small intestine of man in tropical and subtropical areas is associated with chronic diarrhoea and malabsorption especially in severely malnourished children (Gracey 1979). However, bacterial overgrowth of the small intestine is a common finding in apparently normal individuals in less developed countries. Peace Corps volunteers who suffer from diarrhoea, malabsorption and weight loss, also exhibit bacterial proliferation which disappears upon resettlement in an urban sanitary environment (Lindebaum et al 1971). Finally, it is probable that some *Mycoplasma*, *Chlamydia* and other viruses (and viroids?) are involved in the aetiology of diarrhoea.

INTERACTION BETWEEN DIARRHOEAL DISEASES AND MALNUTRITION

The frequent pathogenic infections and the bacterial overgrowth of the small intestine of humans living in poverty reflect the close relationship between the quality of food consumed, the nutritional status and diarrhoea. Probably most diarrhoeas in less developed countries are acquired by ingesting contaminated foods and water. Person-to-person spread by hands, and indirect transmission via utensils, flies, and fomites, also play a role (Table 1.1). Environmental and cultural factors favoring transmission of diarrheal diseases, simultaneously deprive the host of an adequate diet and of the physical and social stimulation required for optimal food utilization.

The interrelation between diarrhoea and malnutrition was not clear until recently, partly because the universal concern with food scarcity led to the belief, without sound evidence, that malnutrition is due to inadequate food consumption alone, without consideration of other environmenatal determinants. When Scrimshaw et al (1959) published their pioneering work on

Table 1.1 Transmission of diarrhoeal disease agents

Anus (faeces) — fingers — mouth
Anus (faeces) — fingers (foods, drinking water, utensils) — mouth
Anus (faeces) — aerosols (fingers, foods, drinking water, utensils, objects) — mouth
Anus (faeces) — fomites (fingers, foods, drinking water) — mouth
Anus (faeces) — soil (water, foods, drinking water, utensils) — mouth
Anus (faeces) — soil (insects, foods, drinking water, utensils) — mouth
Anus — mouth

nutrition-infection interactions, some attention was turned to infectious diseases in the aetiology of malnutrition. The role of infection in the genesis of chronic and severe malnutrition is now recognized by most experienced pediatricians, as had been recognized by Cicely Williams in her classical description of kwashiorkor in the 1930s. Long-term prospective observation of children in their rural ecosytems has now revealed the importance of infectious diseases, particularly diarrhoea, in the development of chronic malnutrition and its acute forms, and in the occurrence of premature death of infants and young children (Mata 1978, Black et al 1982a).

One must consider the intestine as a collection of microbial habitats inhabited by myriads of protozoa, yeasts and bacteria, and also susceptible to being invaded by dozens of helminths, pathogenic bacteria and viruses. The various microbial habitats include the lumen and interplical spaces; plicae and villi which are much more numerous in the duodenum, jejunum, and proximal ileum than in the terminal ileum and colon; intervillous spaces offering opportunities for microbial attachment and for cell invasion; and millions of delicate villi lined by goblet cells, extruding cells and nutrients. In malnutrition, chronic malabsorption and other pathologic processes, there is formation of hollow spaces or microcaverns, possibly permitting stagnation of secretions and cell debris. Bacteria and protozoa associate with crypt cells and dwell in the crypt, or adhere to the villous epithelium, usually at the tips. Agents may be loosely or strongly associated with the host mucosa. *Cryptosporidium* attaches to the brush border of enterocytes, dwelling under the microcalyx. *Giardia* firmly adheres to the mucosal surface and causes anatomical and functional alterations associated with malabsorption. Other agents invade epithelial cells and burrow into the lamina propria, where they cause an inflammatory response with abscess formation and eventual mucosal ulceration. Finally, other micro-organisms translocate to reach the lymph and blood circulation, homing in on distant organs, as in salmonellosis (see Mata 1983b).

It is easy, then, to accept that the close host-parasite interactions will be translated into important physiological and nutritional abnormalities. The negative nutritional effects of diarrhoea are reduced food consumption, reduced nutrient absorption, increased secretion, protein-losing enteropathy, metabolic alterations, growth retardation, and severe energy-protein malnutrition (Table 1.2) (Mata et al 1980).

Reduced food consumption

Diarrhoea interferes with proper consumption of the usual diet, an effect due to one or more of the following symptoms and signs: anorexia, vomiting, dehydration, fever, discomfort, and anxiety. Furthermore, cultural traditions and beliefs often result in parental suppression of foods for days or weeks after an attack of diarrhoea. Prospective observations in cohorts of Guatemalan and Costa Rican rural children living under contrasting en-

Table 1.2 Effect of diarrhoeal disease on the host nutrition, growth and development, and health and survival

Nutrition
Reduced food consumption
Impaired digestion
Impaired absorption
Increased secretion
Metabolic alterations
Growth and development
Acute weight loss
Arrest of linear (height) growth
Progressive wasting and stunting
Impaired interaction with attendants
Impaired learning
Health and survival
Precipitation of severe malnutrition
Impaired immune function
Increased hospitalization, disability and absenteeism
Decreased survival

Table 1.3 Clinical features associated with reduced food consumption, children with diarrhoea observed from birth to 2 years (Puriscal, Costa Rica, 1979–1981)

Diarrhoea	No. of episodes	Number (%) with			
		Anorexia	Fever	Vomiting	Dehydration
Rotavirus	43	15(35)	22(51)	18(42)	4(9)
Campylobacter	17	8(47)	7(41)	6(35)	0
Shigella	6	3(50)	3(50)	0	0
Total	66	26(39)	32(48)	24(36)	4(6)

vironmental conditions revealed that anorexia and vomiting commonly accompany diarrhoea (Table 1.3) often causing severe restriction of food intake for days or weeks (Mata et al 1980). Weekly dietary surveys in weaned children showed that as much as 20 to 50 per cent of the available home diet is not consumed when diarrhoea strikes (Table 1.4) (Mata 1979, Whitehead 1981). Bengali workers demonstrated that the effect had diminished two weeks after recuperation, but was not corrected then, specially in rotavirus and enterotoxigenic *Escherichia coli* (ETEC) diarrhoea (Molla

Table 1.4 Mean daily food consumption during acute diarrhoeal disease in Guatemalan and Ugandan children

Age (months)	Guatemala*				Uganda+	
	Protein (g)		Energy (MJ)		Energy (MJ)	
	Well	*Diarrhoea*	*Well*	*Diarrhoea*	*Well*	*Diarrhoea*
25–30	25	19	3.82	3.02	3.52	1.89
31–36					3.95	2.03
% Change well-diarrhoea		24		21		48

* After Mata (1979)
+After Whitehead (1981)

et al 1983a). This observation is particularly relevant to developing countries, because children who are chronically malnourished frequently consume quantities of food that are just adequate for normal growth.

Reduced absorption of nutrients

Diarrhoea impairs consumption and absorption of macronutrients, an effect persisting for several weeks after the episode. Adhesion of bacteria to the mucosa, release of enterotoxins, direct damage to the enterocyte and crypt cells, bacterial hydrolysis of bile acids and carbohydrates, and other pathogenic actions result in a diminished capacity of the mucosa to absorb macro- and micronutrients. Molla and coworkers (1983b) recently showed a decreased absorption of nitrogen, calories, fat, and carbohydrate in children with specific diarrhoeas, an effect partially corrected eight weeks after termination of the episode.

Increased secretion

Diarrhoea is also a state of hypersecretion. In rotavirus infection there is a clear movement of water from the infected segment of the small intestine into the lumen, resulting in a decreased sodium flux from the lumen to the extracellular fuid (e.c.f.) and an increased sodium flux from the e.c.f. into the lumen (Field 1976). These alterations are related to damage and lysis of villous tips with replacement of absorptive enterocytes by immature crypt cells. There is no alteration of cyclic adenosine monophosphate (CMP) concentrations. Other causes of hypersecretion are stimulation of cyclic AMP and cyclic guanosine monophosphate (GMP) by heat-labile toxins and heat-stable toxins released by enteric bacteria, or by increased bile and fatty acids from bacterial metabolism, or by hormones and neurotransmitters (Table 1.2). The hypersecretory state results in important deficits in sodium, potassium, chloride, and water, and probably in other elements such as vitamins and trace elements.

Nutrient losses

Similar to the abrupt fall in plasma albumin observed after an attack of measles, a 'protein-losing enteropathy' occurs after structural alterations in the mucosal epithelium caused by *shigella*, rotaviruses, and probably *campylobacter*, *yersinia* and *cryptosporidium*. An increased ratio of α_1-antitrypsin (stool over serum concentrations) was observed in about half of rotavirus diarrhoeas and even more frequently in shigellosis (Rahaman & Wahed 1983). The consequences for malnourished children might be more serious, because in chronic malnutrition there is already a marked thinning of the intestinal wall. The protein-losing enteropathy might help to explain the outbreaks of kwashiorkor that follow by a few weeks the epidemics of diar-

rhoea. Other metabolic alterations, such as those described in systemic infections, are expected: negative balances of nitrogen, magnesium, potassium, and phosphorus; mobilization of amino acids from muscle for gluconeogenesis; augmented synthesis of acute-phase reactant proteins; and sequestration of trace elements.

Effect on growth and development

Diarrhoea induces acute weight loss and arrest in linear growth, as do other infections. Detailed observation of this phenomenon was possible by prospective studies of children in their natural village ecosystems in Guatemala, the Gambia, Uganda, Bangladesh and Costa Rica (Mata 1978, Martorell et al 1980, Cole & Parkin 1977, Black et al 1982a, Mata 1982). Inspection of individual growth curves of 45 cohort children showed a consistent pattern of relative absence of diarrhoea during exclusive breastfeeding; the nutritional status of infants was adequate, even in those that had experienced fetal growth retardation or were born prematurely (Mata, 1979; Mata, 1982). With the onset of weaning (a protracted process starting at about 3 to 6 months of life and continuing throughout the second year of life) a variety of infections associated with faltering of the weight and height curves were recorded in each child (Mata 1978). Previous description of 20 growth histories selected among the 45 cohort children revealed a consistent pattern of progressive weight deterioration (wastage) with infections. Figure 1.1 depicts the weight curve (compared to the Boston-Iowa 50th percentile), intestinal infections, illnesses and growth increments of a typical Guatemalan village child during his first 3 years of life (Mata et al 1971). This particular boy grew well during the first 6 to 7 months of life, a period characterized by intensive and almost exclusive breast-feeding, and by uncommon and transient enteric infections. *Giardia* appeared at about 6 months of age, but enteroviruses were isolated from early life. Weaning in this particular child peaked at 18 months, and this was accompanied by frequent infections with a variety of enteric agents. This child had in the first 3 years of life: 4 weeks with adenoviruses, 84 with enteroviruses, 8 with *Shigella*, 1 with enteropathogenic *Escherichia coli*, 18 with *Entamoeba histolytica*, 12 with *Giardia*, and 52 with *Ascaris*. He also had 5 weeks with rotaviruses (Mata et al 1983). The child suffered from a continuum of diarrhoeal and respiratory diseases. Weight faltered after six months of age and did not improve during the whole weaning period (6 to 18 months). Thereafter a relative catch-up was observed, but at the end of the third year of life, weight losses were recorded in conjunction with diarrhoea and bronchopneumonia. The child survived the hazards of early childhood, but died of typhoid fever during school years. Similar children succumbed in early childhood (Mata 1978).

The wasting and stunting effect of diarrhoea was more marked in children who had experienced fetal growth retardation, a common event in Guatemalan Indian villages (Mata et al 1980). A negative effect of diarrhoea on

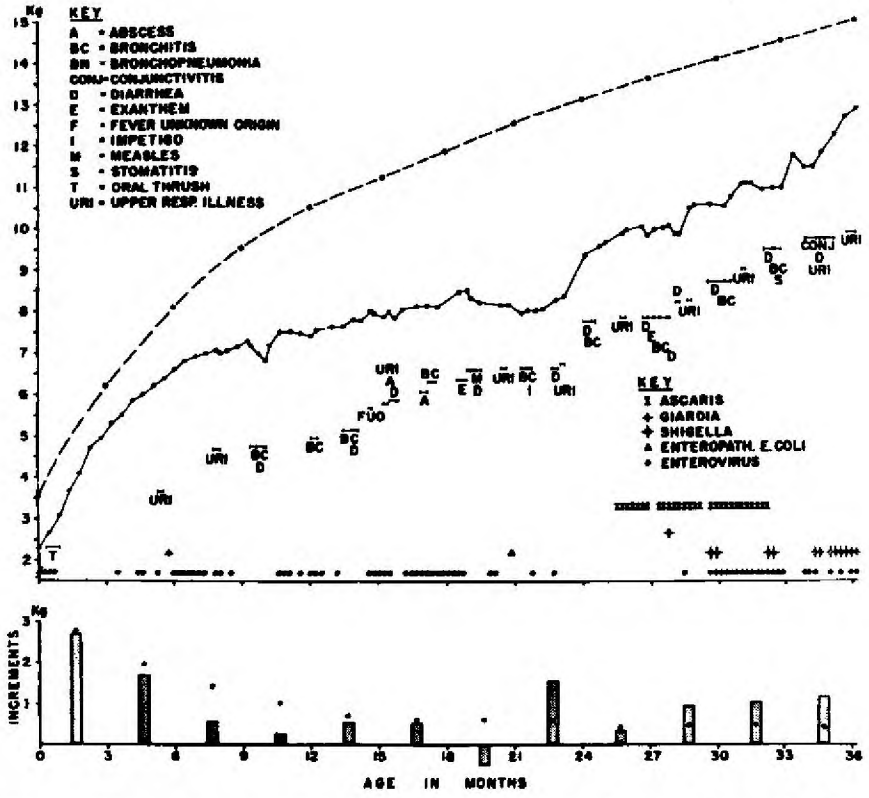

Fig. 1.1 Weight curve, enteric infections and infectious diseases in male child no. 12 of the Cauqué study. *Top*: Broken line is the 50th percentile of the Boston-Iowa growth standard; continuous line is the weight curve of the child. Horizontal bars indicate episodes of disease, and length of bars their duration .Each mark shows a week positive for a particular infectious agent. Note that acute diarrhoeal and acute respiratory infections often occur simultaneously or in succession. *Bottom*: Observed trimester weight increments in the child (vertical bars) and expected median increments of the standard curve (dots). (After Mata et al 1971.)

growth has been described in several other studies. On the other hand, wasted and/or stunted children are prone to suffer from a more severe course of diarrhoea and also exhibit a higher risk of death, as evidenced in field studies in Guatemala, India, Bangladesh and The Gambia (Table 1.5) (Chen et al 1980). Thus, diarrhoea is a malnourishing event, and malnutrition in turn enhances the risk of dying from infection, a costly vicious circle.

THE GLOBAL PROBLEM OF DIARRHOEA

Morbidity estimates

Few studies to measure diarrhoeal diseases morbidity have been conducted. Furthermore, the few available studies used different field methodologies

Table 1.5 Mortality rate according to nutritional status, preschool children, Bangladesh, 1975–1976

Nutritional status as % of Harvard values	Number of children	Deaths per 1000 children 0–11*	12–23*
Weight/height			
>90	399	35.1	17.5
80–89	979	26.6	26.6
70–79	566	28.3	21.2
<70	75	66.7	80.0
Height/age			
>95	182	16.5	16.5
90–94	656	22.9	16.8
85–89	713	28.0	9.8
<85	468	51.3	62.0

*Months after anthropometric assessment
Adapted from Chen et al (1980)

and do not necessarily reflect the world-wide situation. The prospective field study in a small Mayan village in Guatemala concluded that children suffer about eight episodes of diarrhoea per child per year during the first three years of life (Mata et al 1978). A similar figure has been recorded for children also studied prospectively in Matlab, Bangladesh (Black et al 1982a). More recently, even higher rates than those of Cauqué and Matlab were found in Brazilian children by Dr Richard Guerrant (personal communication).

Rohde & Northrup (1976) estimated for 1975, 500 million cases of diarrhoea for children less than 5 years in Africa, Asia and Latin America, an estimate that could well reflect only acute and severe attacks. Another conservative estimate based on 3 studies that employed bi-monthly home visits for surveillance yielded 460 million cases of diarrhoea for 1975, roughly about 1 episode per child per year. However, using the Cauqué data obtained through weekly surveillance, the resulting figure is about 2 billion cases per year (Mata et al 1980). A more recent estimate of the global morbidity based on 5 studies yielded, for 1980, about 1000 million episodes for children under 5 years of age (Snyder & Merson 1982).

Mortality estimates

An investigation into the causes of death in 4 Guatemalan rural communities in 1956–1957, revealed that 43 per cent of the diarrhoeal deaths were not recorded at all in the official vital statistics (Béhar et al 1958). Thus, figures for diarrhoeal disease deaths probably are understimated in less developed countries, although registration of the event and cause has steadily improved over recent years in most nations.

Global estimates of diarrhoeal disease mortality have ranged from 5 to 18

million deaths for children under 5 years of age in 1975 for Africa, Asia and Latin America (Rhode & Northrup 1976). Different ways to estimate the diarrhoea death toll coincided in establishing about 5 million deaths per year, which correspond to about 30 per cent of all deaths in the 0–5 year age group (Puffer & Serrano 1973, Barua 1981, Snyder & Merson 1982).

There is even less information on the relative contribution of the specific diarrhoeas to global morbidity and mortality, and not one single study can be considered representative of the urban and rural situation of any country. The aetiology of diarrhoea varies according to urban or rural setting, season, and level of environmental sanitation and personal hygiene. When these factors are deficient, shigellosis and enterotoxigenic diarrhoeas become very common and are dangerous (Black et al 1982b, Mata et al 1983). The toxic shigellosis and dehydrating bacterial and rotaviral diarrhoeas are likely to account for most deaths in the poor urban settings. The severity and outcome of all diarrhoeas is aggravated by low birth weight, premature weaning, child neglect and other social aberrations that seem to occur more frequently in urban than in rural settings.

Mortality in the Americas

The data of diarrhoeal disease mortality for Latin America appears to be fairly complete (OPS 1980, WHO 1982) as compared to those for Africa. Marked differences are noted between the very low rate in North America and in the rest of the continent (Table 1.6). The highest rate corresponds to Middle America (Mexico and the six Republics of the Isthmus) and tropical South America (which excludes Argentina, Chile, Uruguay and Paraguay). However, even in the Caribbean and in temperate South America, diarrhoea deaths account for a significant part of the total mortality among infants and young children. Thus, diarrhoeal diseases still are a leading cause of death in the Americas (Table 1.7) including the United States and Canada where they ranked 5th as recently as 1976 (OPS 1980, WHO 1982).

Table 1.6 Diarrhoeal disease mortality in the Americas (per 100 000) and proportionate mortality (%), by age, 1976

Region	Age (years) <1		1–4	
	Rate	%	Rate	%
North (without Mexico)	19	1.4	0.6	0.9
Caribbean	439	15.2	28	15.0
Middle America	1078	22.8	154	25.8
South, tropical	1066	20.3	151	21.5
South, temperate	496	10.9	20	9.1

Adapted from Organización Panamericana de la Salud 1980

Table 1.7 Rank of diarrhoeal disease as a cause of death in the Americas, 1976

Region	Number of nations	Cause of death 1st	2nd	3rd	4th	5th
North (without Mexico)	2					1
Caribbean	7		4		3	
Middle America	7	3	2	2		
South, tropical	5	2	3			
South, temperate	3		1	1	1	

Adapted from Organización Panamericana de la Salud 1980

THE GLOBAL PROBLEM OF MALNUTRITION

There is no quantitative information about the contribution of diarrhoeal disease to the genesis of chronic and severe malnutrition, although there is adequate evidence attesting to its contributory role. Cross-cultural studies of mortality and long-term prospective observations have shown the frequent association of diarrhoea and malnutrition in the event of death. The Pan American Study of Childhool Mortality reveled that low birth weight, premature weaning, and postnatal malnutrition were correlates in most diarrhoeal deaths (Puffer & Serrano 1973).

During 8 years of prospective observations on all infants and preschool children in a typical Guatemalan village, 58 child deaths (excluding neonatal) were recorded of which 11 (19 per cent) were diarrhoea-associated and 4 (7 percent) were malnutrition-associated; 3 of the deaths were attributed to both diarrhoea and malnutrition (Mata 1978). In this study, the proficiency of the peadiatrician (Dr J. J. Urrutia) and his field staff probably prevented many deaths from malnutrition and diarrhoea.

It is logical, then, to accept that diarrhoeal disease is a significant contributor to the global rates of malnutrition. The world prevalence of malnutrition compiled by the Nutrition Unit of the World Health Organization is shown in Table 1.8. There seems to be no doubt that a significant proportion of childhood malnutrition is directly or indirectly due to the high rates of diarrhoeal disease prevalent in in the same regions where malnutrition exists. Protein-energy malnutrition is exposed or aggravated in certain regions and countries by food shortages. Nevertheless, since most of the wasting and stunting observed in less developed countries is confined to infants and preschool children, who also are the most severely affected by diarrhoeal and other infectious diseases, a strong causal relationship between infection and malnutrition is sought (Mata 1982).

Iron-deficiency anaemias also are complicated by infections, and in many cases are caused entirely by them (e.g. hookworm infection). Regarding low birth weight, the stunting of child-bearing women frequently is the result of chronic malnutrition and this, in turn, may be induced by repetetive infections during childhood. Therefore, early infectious experiences in child-

Table 1.8 Prevalence of nutritional deficiencies in the developing world

	Africa	Asia*	The Americas§
Low birth weight	15*	27	11
	(3)	(13)	(1)
Weight deficit, preschool children	30	47‡	28
	(20)	(94)	(13)
Stunting, preschool children	35	40‡	43
	(24)	(81)	(20)
Iron-deficiency anemia, women	40	58	17
	(37)	(172)	(13)

* Percentage; in parentheses, millions of persons
* Excluding China
‡ Weighted for India
§ Excluding Argentina, Chile, Uruguay and Paraguay
Adapted from WHO A36/7 (1983)

hood must have a late indirect repercussion during reproductive age by favouring low birth weight.

Infectious diarrhoea has been recognized as a precipitating factor of severe malnutrition, especially the oedematous form; severe eye manifestations of vitamin A deficiency often appear following diarrhoea and other infectious diseases like measles.

CONTROL OF DIARRHOEAL DISEASES AND MALNUTRITION

There is no doubt that the control and prevention of diarrhoeal diseases will rapidly lead to improved levels of child nutrition and survival. The comparison of diarrhoeal disease death rates throughout the world provides a clue to the marked reduction in mortality in several countries in recent times. Data for the Americas for the period 1967–1977 permit estimation of the change in mortality rates throughout the span. The mean percent annual variation in diarrhoeal disease mortality, for most Latin American countries, indicates a marked decline in mortality (Fig. 1.2) (Mata 1983a). No definitive explanation is available for that behaviour, particularly because the trend was evident before the advent or oral rehydration. Greater information of the public about the nature and perils of diarrhoea, sustained improvements in income, education, nutrition, housing and hygiene, and gains in family planning and child spacing must have contributed to the declines in mortality in Cuba, Costa Rica, Jamica, Trinidad and Venezuela.

Diarrhoeal disease mortality is a main contributor to infant mortality, and both variables are highly correlated (Mata et al 1980). Therefore, if deaths due to diarrhoea decrease, so will infant deaths. This observation was clearly documented in Costa Rica (Mata 1983) permitting forecasts of fluctuations in infant mortality as a consequence of variations in diarrhoeal disease deaths. These observations provide further justification to emphasize control programes using the present knowledge on the epidemiology, aetiology and

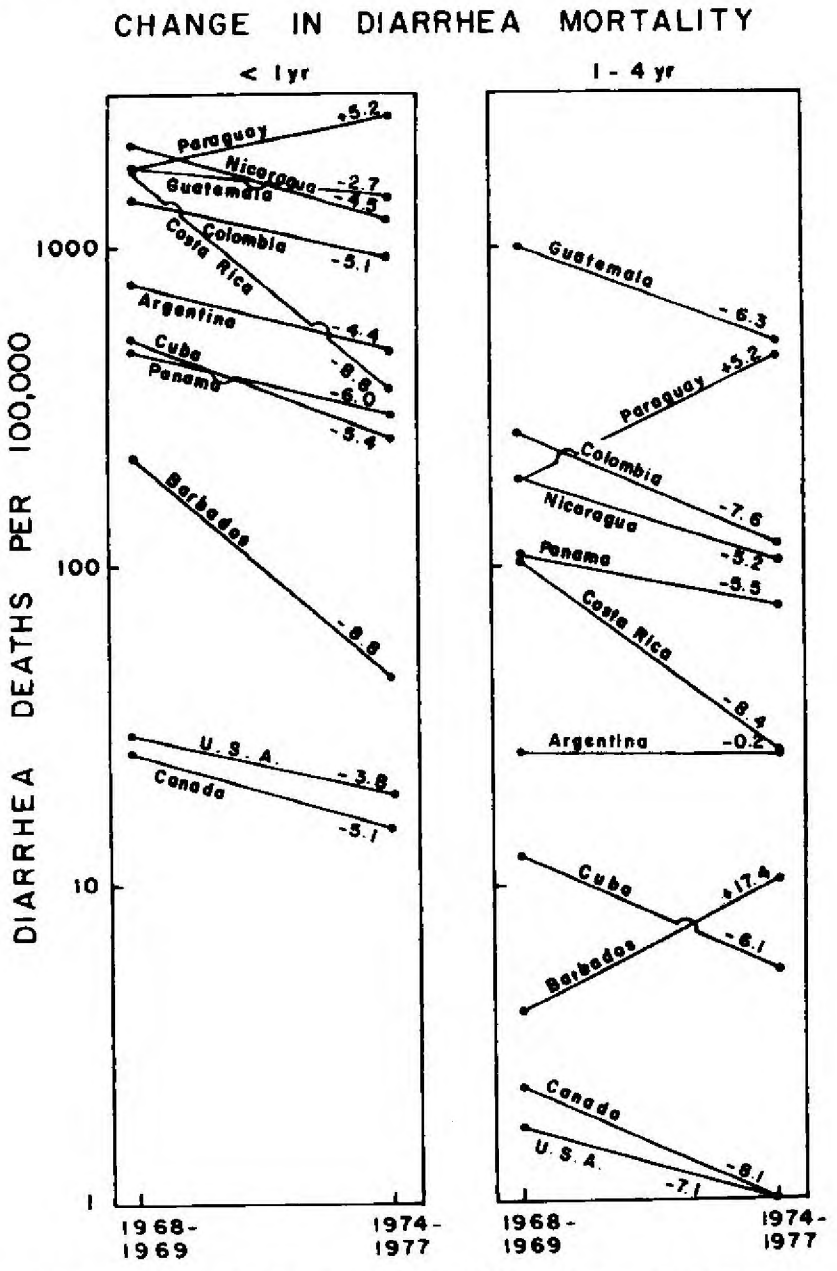

Fig. 1.2 Mortality due to diarrhoeal diseases, per 100 000 population, for infants and preschool children, selected countries of the Americas. The following should be noted: (a) marked differences in rates for the various countries; (b) consistent declines in mortality for most countries over the period 1968–69 to 1974–77. The mean per cent annual variation is shown next to the name of the country, and it generally negative, except for countries where a deterioration of diarrhoeal mortality appears to have occurred, for instance, in Paraguay and Barbados. The graph was prepared using official data published by the Pan American Health Organization (OPS 1980, WHO 1982).

treatment of the diarrhoeal diseases (Feachem & Koblinsky 1983, Feachem et al 1983, Mata 1983).

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